JAPANESE PATENT OFFICE
PATENT JOURNAL (A)
KOKAI PATENT APPLICATION NO. HEI 11[1999]-130753

Int. Cl.[6]:	C 07 D 231/12 233/60 249/08 277/24 401/04 C 07 D 403/04 417/04 //A 61 K 31/41 31/415 31/425 31/44
Filing No.:	Hei 9[1997]-300384
Filing Date:	October 31, 1997
Publication Date:	May 18, 1999
No. of Claims:	3 (Total of 29 pages; OL)
Examination Request:	Not filed

PHENYLCARBOXYLIC ACID DERIVATIVES

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[There are no amendments to this patent.]

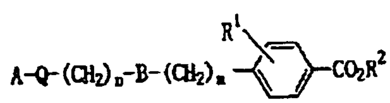
Abstract (revised)

Problem

To present novel compounds useful as medicines that can simultaneously reduce triglycerides and cholesterol in the blood by the action of inhibiting fatty acid biosynthesis and cholesterol biosynthesis simultaneously, are highly stable, and have not yet been published in the literature.

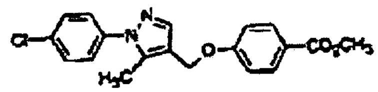
Means to solve

General Formula (I)



(I)

Concretely, phenylcarboxylic acid derivatives represented by, for example,

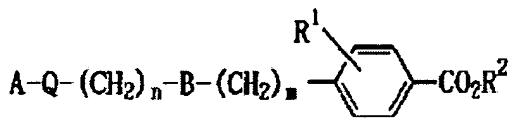


and their salts.

Claims

1. Phenylcarboxylic acid derivatives represented by General Formula (I)

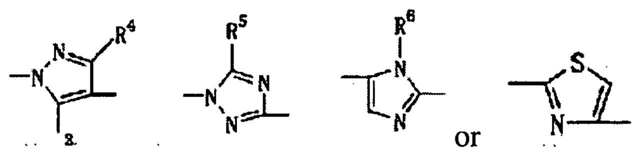
[Structure 1]



(I)

(wherein A denotes a lower alkyl group, or optionally substituted phenyl group or optionally substituted pyridyl group that may have as substituent, groups selected from halogen atoms, lower alkyl groups, lower alkoxy groups and amino groups in which hydrogen atoms on the nitrogen atom have been substituted with lower alkyl groups, Q denotes

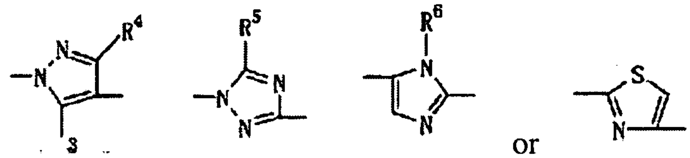
[Structure 2]



(wherein R^3 and R^4 are the same or different and denote hydrogen atoms, lower alkyl groups, amino groups in which the hydrogen atoms on the nitrogen atom may be substituted with lower alkyl groups, or pyrrole groups, R^5 and R^6 each denote hydrogen atoms or lower alkyl groups), B denotes an oxygen atom or NR^7 (wherein R^7 denotes a hydrogen atom or lower alkyl group), R^1 denotes a hydrogen atom, halogen atom or lower alkoxy group, R^2 denotes a hydrogen atom or lower alkyl group, n denotes 1 or 2, and m denotes 0 or 1), and their salts.

2. Phenylcarboxylic acid derivatives described in Claim 1 wherein A is an optionally substituted phenyl group that may have as substituent, groups selected from halogen atoms, lower alkyl groups, lower alkoxy groups and amino groups in which hydrogen atoms on the nitrogen atom have been substituted with lower alkyl groups, Q is

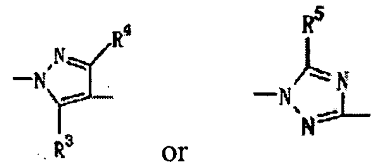
[Structure 3]



(wherein R^3 and R^4 are the same or different and denote hydrogen atoms or lower alkyl groups, and R^5 and R^6 each denote lower alkyl groups), B is an oxygen atom, R^1 is a hydrogen atom, R^2 is a hydrogen atom or lower alkyl group, n is 1 and m is 0, and their salts.

3. Phenylcarboxylic acid derivatives described in Claim 2 wherein A is a phenyl group or a phenyl group substituted with a halogen atom, Q is

[Structure 4]



(wherein R^3 denotes a methyl group, R^2 denotes a hydrogen atom, and R^5 denotes a methyl group), and their salts.

Detailed explanation of the invention

[0001]

Technical field of the invention

This invention pertains to novel phenylcarboxylic acid derivatives and their pharmaceutically acceptable salts. Said phenylcarboxylic acid derivatives and their salts act to simultaneously inhibit fatty acid biosynthesis and cholesterol biosynthesis and are useful as antihyperlipidemia agents.

[0002]

Prior art

It is now becoming clear that by lowering triglycerides (abbreviated as TG below) and low-density lipoprotein-cholesterol, which are serum lipids, occurrence of coronary artery disease can be reduced. For example, the United Airline Trial (Krasno, L.R. and Kidera, G.J.: Journal of the American Medical Association, 219, 845, 1972) using clofibrate, which is a TG-reducing agent, proved that it can significantly reduce myocardial infarctions. And the West of Scotland Coronary Prevention Study (Shepherd, J., et al.: New England Journal of Medicine,

333, 1301, 1995) using plavastatin, which is a 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor that reduces cholesterol, proved that it reduced coronary artery disease and reduced mortality.

[0003]

Consequently, if TG and cholesterol could be reduced strongly at the same time, it is anticipated that coronary artery disease could be reduced and mortality could be reduced.

[0004]

Previously, compounds that inhibit fatty acid biosynthesis and reduce TG and simultaneously inhibit cholesterol biosynthesis have been published in, for example, Japanese Kokai Patent Application Nos. Hei 2[1990]-56452, Hei 3[1991]-275666, Hei 4[1992]-111773, Hei 4[1992]-242887, Hei 4[1992]-243228, Hei 5[1993]-519129, Hei 5[1993]-507962, and Hei 5[1993]-140826. However, useful drugs have not yet been reported.

[0005]

Problems to be solved by the invention

The main goal of this invention is to present novel compounds useful as medicines that can simultaneously reduce triglycerides and cholesterol in the blood by the action of simultaneously inhibiting fatty acid biosynthesis and cholesterol biosynthesis, are highly stable, and have not yet been published in the literature.

[0006]

Means to solve the problems

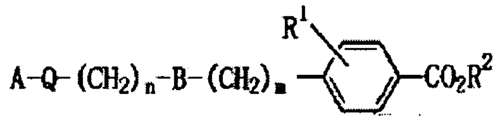
Upon diligent research in view of said circumstances, the inventors discovered that phenylcarboxylic acid derivatives represented by General Formula (I) below and their pharmaceutically acceptable salts have simultaneously act to inhbit fatty acid biosynthesis and cholesterol biosynthesis, and completed this invention.

[0007]

That is, this invention pertains to phenylcarboxylic acid derivatives represented by General Formula (I)

[0008]

[Structure 5]



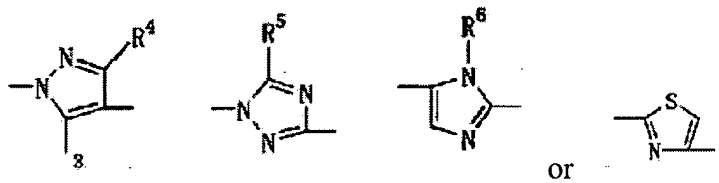
(I)

[0009]

(wherein A denotes a lower alkyl group, or optionally substituted phenyl group or optionally substituted pyridyl group that may have as substituent, groups selected from halogen atoms, lower alkyl groups, lower alkoxy groups and amino groups in which hydrogen atoms on the nitrogen atom have been substituted with lower alkyl groups, Q denotes

[0010]

[Structure 6]



[0011]

(wherein R^3 and R^4 are the same or different and denote hydrogen atoms, lower alkyl groups, amino groups in which the hydrogen atoms on the nitrogen atom may be substituted with lower alkyl groups, or pyrrole groups, R^5 and R^6 each denote hydrogen atoms or lower alkyl groups), B denotes an oxygen atom or NR^7 (wherein R^7 denotes a hydrogen atom or lower alkyl group), R^1 denotes a hydrogen atom, halogen atom or lower alkoxy group, R^2 denotes a hydrogen atom or lower alkyl group, n denotes 1 or 2, and m denotes 0 or 1), and their salts.

[0012]

Embodiments of the invention

For the lower alkyl groups denoted by A, R^2, R^3, R^4, R^5, R^6 or R^7 in General Formula (I) above, C_{1-4} straight chain or branched chain alkyl groups can be cited. Concretely, methyl groups, ethyl groups, n-propyl groups, isopropyl groups, n-butyl groups, isobutyl groups, sec-butyl groups, tert-butyl groups, etc., can be cited.

[0013]

For halogen atoms denoted by A or R^1, fluorine atoms, chlorine atoms, bromine atoms, and iodine atoms can be cited.

[0014]

For lower alkoxy groups denoted by A or R^1, C_{1-4} straight chain alkoxy groups can be cited. Concretely, methoxy groups, ethoxy groups, n-propoxy groups and n-butoxy groups can be cited.

[0015]

For amino groups in which hydrogen atoms on the nitrogen atom may be substituted with lower alkyl groups denoted by R^3 or R^4, in addition to amino groups, amino groups in which 1 or 2 of the 2 hydrogen atoms of the amino group have been substituted with the above lower alkyl groups can be cited. Concretely, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-(n-propyl)amino, N,N-di-(n-propyl)amino, N-(n-butyl)amino, N,N-di(n-butyl)amino groups, etc., can be cited.

[0016]

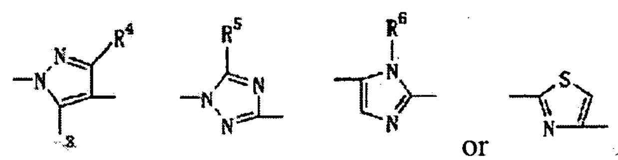
For the various substituents of the phenyl group and pyridyl group in the "optionally substituted phenyl group or optionally substituted pyridyl group that may have as substituent, groups selected from halogen atoms, lower alkyl groups, lower alkoxy groups and amino groups in which hydrogen atoms on the nitrogen atom have been substituted with lower alkyl groups" denoted by A, the same halogen atoms, lower alkyl groups, lower alkoxy groups and amino groups in which hydrogen atoms on the nitrogen atom have been substituted with lower alkyl groups as above can be cited. More concretely, for optionally substituted phenyl groups and optionally substituted pyridyl groups, phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, 4-iodophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-propylphenyl, 3-propylphenyl, 4-propylphenyl, 4-aminophenyl, 3-aminophenyl, 2-aminophenyl, 4-(N-methyl)aminophenyl, 3-(N-methyl)aminophenyl, 2-(N-methyl)aminophenyl, 4-(N,N-dimethyl)aminophenyl, 3-(N,N-dimethyl)aminophenyl, 2-(N,N-dimethyl)aminophenyl, 4-(N-ethyl)aminophenyl, 3-(N-ethyl)aminophenyl, 2-(N-ethyl)aminophenyl, 4-(N,N-diethyl)aminophenyl, 3-(N,N-diethyl)aminophenyl, 2-(N,N-diethyl)aminophenyl, 4-(N-(n-propyl))aminophenyl, 3-(N-(n-propyl))aminophenyl, 2-(N-(n-propyl))aminophenyl, 4-(N,N-di-(n-propyl))

amino phenyl, 3-(N,N-di-(n-propyl)) aminophenyl, 2-(N,N-di-(n-propyl)) aminophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-(n-propoxy)phenyl, 3-(n-propoxy)phenyl, 4-(n-propoxy)phenyl, 2-isopropoxyphenyl, 3-isopropoxyphenyl, 4-isopropoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-chloro-2-pyridyl, 4-fluoro-2-pyridyl, 4-bromo-2-pyridyl groups, etc., can be cited.

[0017]

Of the phenylcarboxylic acid derivatives of this invention that are represented by General Formula (I), favorable compounds are compounds wherein A is an optionally substituted phenyl group that may have as substituent, groups selected from halogen atoms, lower alkyl groups, lower alkoxy groups and amino groups in which hydrogen atoms on the nitrogen atom have been substituted with lower alkyl groups, Q is

[0018]
[Structure 7]



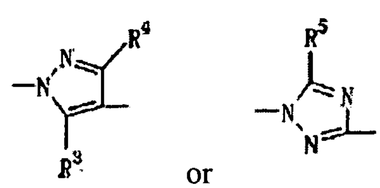
[0019]

(wherein R^3 and R^4 are the same or different and denote hydrogen atoms or lower alkyl groups, R^5 and R^6 each denote lower alkyl groups), B is an oxygen atom, R^1 is a hydrogen atom, R^2 is a hydrogen atom or lower alkyl group, n is 1 and m is 0.

[0020]

More favorable phenylcarboxylic acid derivatives (I) are compounds among the above favorable compounds wherein A is a phenyl group or phenyl group substituted with halogen atom, Q is

[0021]
[Structure 8]



[0022]

(wherein R^3 denotes a methyl group, R^4 denotes a hydrogen atom and R^5 denotes a methyl group).

[0023]

Particularly favorable phenylcarboxylic acid derivatives (I) are compounds wherein A is a phenyl group or 4-chlorophenyl group, and R^2 is a hydrogen atom, methyl group or ethyl group.

[0024]

As concrete examples of particularly favorable phenylcarboxylic acid derivatives (I), for example, the following compounds can be cited.

[0025]

· 1-phenyl-5-methyl-4-(4'-methoxycarbonylphenoxy)methylpyrazole
· 1-(4-chlorophenyl)-5-methyl-4-(4'-ethoxycarbonylphenoxy)methylpyrazole
· 1-(4-chlorophenyl)-5-methyl-4-(4'-carboxyphenoxy)methylpyrazole
· 1-(4-chlorophenyl)-5-methyl-3-(4'-methoxycarbonylphenoxy)methyl-1,2,4-triazole

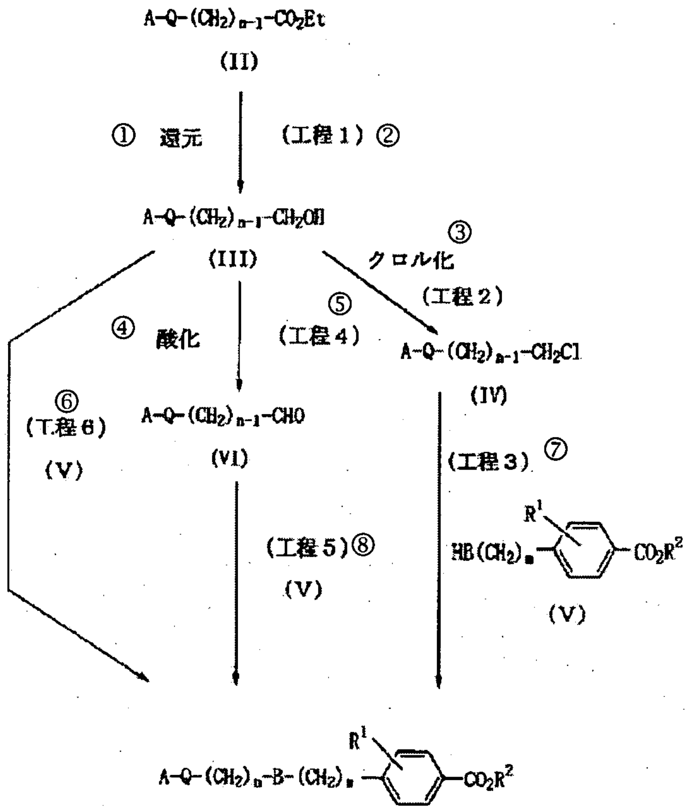
There are no particular restrictions on salts of the phenylcarboxylic acid derivatives represented by General Formula (I) above. Acid adduct salts and/or basic salts in which pharmaceutically acceptable acidic and/or basic compounds have been used can be cited. For these acid adduct salts, for example, salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid or hydrobromic acid; and salts with organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, acetic acid, p-toluenesulfonic acid, or methanesulfonic acid can be cited. For basic salts, for example, salts with alkali metals or alkaline-earth metals such as sodium, potassium, magnesium or calcium; and salts with amines such as ammonia, methylamine, dimethylamine, piperidine, cyclohexylamine, or triethylamine can be cited.

[0026]

The phenylcarboxylic acid derivatives (I) of this invention can be manufactured, for example, by the synthetic routes shown in the reaction equations below.

[0027]

[Structure 9]



Key:

Key:	1	Reduction
	2	(Process 1)
	3	Chlorination (Process 2)
	4	Oxidation
	5	(Process 4)
	6	(Process 6)
	7	(Process 3)
	8	(Process 5)

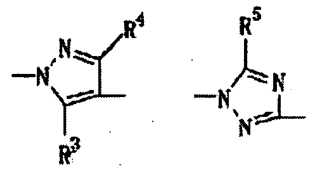
[0028]

(wherein A, Q, B, R^1, R^2, n and m are the same as above.)

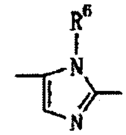
Among the phenylcarboxylic acid derivatives of General Formula (I), compounds in which Q is

[0029]

[Structure 10]



or



[0030]

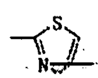
can be synthesized, for example, using the well-known starting material (II) in the above reaction equations by a (Process 1) → (Process 2) → (Process 3) → General Formula (I) route, a (Process 1) → (Process 4) → (Process 5) → General Formula (I) route, or a (Process 1) → (Process 6) → General Formula (I) route.

[0031]

Among the phenylcarboxylic acid derivatives of General Formula (I), compounds in which Q is

[0032]

[Structure 11]



[0033]

can be synthesized, for example, using the well-known starting material (IV) in the above reaction equations with a (Process 3) → General Formula (I) route, or using the well-known compounds (III) with a (Process 6) → General Formula (I) route.

[0034]

To be more specific, the various processes in the above reaction equations are carried out as follows.

[0035]

(Process 1)

By reducing well-known compounds represented by General Formula (II) above, compounds represented by General Formula (III) can be manufactured. There are no particular restrictions on reducing agents used in this reaction. Aluminum lithium hydride ($LiAlH_4$),

sodium borohydride ($NaBH_4$), lithium borohydride ($LiBH_4$), sodium dihydrobis(2-methoxyethoxy)aluminum ($NaAlH_2(OCH_2CH_2OCH_3)_2$), sodium borohydride – Lewis acid systems, aluminum lithium hydride – Lewis acid systems, etc., can be cited. There are no particular restrictions on these Lewis acids. Aluminum chloride, zinc chloride, boron trifluoride – diethyl etherate ($BF_3 - Et_2O$), etc. can be cited. This reaction is normally performed in an appropriate solvent. There are no particular restrictions on the solvents used as long as they do not participate in the reaction. For example, aromatic hydrocarbons such as benzene, toluene, or xylene, and ethers such as diethyl ether, tetrahydrofuran, dioxane or diglyme can be cited. For the reducing agent, the use of about 0.5-3 molar equivalents with respect to 1 mol of General Formula (II) compound is appropriate. The reaction temperature is approximately 0°C – the boiling point of the solvent or so, preferably about 10°C-50°C. The reaction time is about 0.1-6 h, preferably about 0.5-2 h.

[0036]

Compounds of General Formula (III) obtained from this reaction can be used in Process 2, Process 4 and Process 6 with or without isolation.

[0037]

(Process 2)

By reacting compounds represented by the above General Formula (III) with a chlorinating agent without solvent or in an appropriate solvent, compounds represented by General Formula (IV) can be manufactured. There are no particular restrictions on solvents as long as they do not participate in the reaction. For example, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran or dioxane, halogenated hydrocarbons such as dichloromethane, or chloroform, and aprotic polar solvents such as acetonitrile can be used. There are no particular restrictions on the chlorinating agents used in this invention. Chlorine gas, thionyl chloride, sulfuryl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, etc., can be cited. About 1-10 molar equivalents, preferably about 1-1.5 molar equivalents, per 1 mol of compound of General Formula (III) should be used. The reaction temperature should be approximately –10°C – the boiling point of the solvent so, preferably 0-50°C. The reaction time is about 0.1-6 h, preferably about 0.5-2 h.

[0038]

Compounds of General Formula (IV) obtained from this reaction can be used in Process 3 with or without isolation.

[0039]

(Process 3)

By reacting compounds represented by General Formula (IV) above and compounds wherein R^2 in General Formula (V) is a lower alkyl group with basic compounds in an appropriate solvent, compounds wherein R^2 in General Formula (I) is a lower alkyl group can be manufactured. There are no particular restrictions on solvents as long as they do not participate in the reaction. For example, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran or dioxane, halogenated hydrocarbons such as dichloromethane or chloroform, and aprotic polar solvents such as acetonitrile, dimethylformamide, dimethylacetamide, or dimethyl sulfoxide can be used. For basic compounds, for example, organic basic compounds like tertiary amines such as triethylamine or pyridine, and inorganic basic compounds like alkali metal carbonate salts such as sodium carbon or potassium carbonate, alkali metal bicarbonate salts such as sodium bicarbonate or potassium bicarbonate, alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metals such as sodium or potassium, and alkali metal hydrides such as sodium hydride can be cited. About 0.9-2 molar equivalents, preferably 1-1.2 molar equivalents of compounds represented by General Formula (V) with respect to 1 mol of General Formula (IV) compounds should be used. About 1-10 molar equivalents, preferably 1-2 molar equivalents of basic compounds with respect to 1 mol of General Formula (IV) compounds should be used. The reaction temperature is approximately 0°C – the boiling point of the solvent, preferably about 0-50°C. The reaction time is about 0.5-48 h, preferably about 1-12 h.

[0040]

(Process 4)

By reacting compounds represented by General Formula (III) above with an oxidizing agent in an appropriate solvent, compounds represented by General Formula (VI) can be manufactured. There are no particular restrictions on solvents used here as long as they do not participate in the reaction. For example, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran or dioxane, halogenated hydrocarbons such as dichloromethane or chloroform, alkyl ketones such as acetone, methyl ethyl ketone, or methyl isobutyl ketone, and aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile and dimethyl sulfoxide can be cited. There are no particular restrictions on the oxidizing agents and various oxidizing agents can be used. For oxidizing agents that contain chromic acid, for example, chromic acid, pyridinium chlorochromate and pyridinium dichromate can be cited. For oxidizing agents containing electrophilic agents and dimethyl sulfoxide, for example, acetic anhydride, trifluoroacetic anhydride, phosphorus

pentaoxide, sulfur trioxide – pyridine complex and oxalyl chloride can be used for the electrophilic agent. For oxidizing agents containing manganese, manganese dioxide can be cited. Oxidizing agents of hypochlorous acid or dimethyl sulfide-N-chlorosuccinimide can also be used. About 1-50 molar equivalents, preferably about 1-2 molar equivalents of oxidizing agent with respect to 1 mol of General Formula (III) compound should be used. The reaction temperature is about –78 to 30°C. The reaction time is about 0.1-48 h, preferably about 0.5-12 h. Compounds of General Formula (VI) obtained by this reaction can be used for Process 5 with or without isolation.

[0041]

(Process 5)

By reacting compounds represented by General Formula (VI) above and compounds wherein R^2 in General Formula (V) is a lower alkyl group with a reducing agent in an appropriate solvent, compounds wherein R^2 in General Formula (I) is a lower alkyl group can be manufactured. There are no particular restrictions on solvents used here as long as they do not participate in the reaction. Alcohols such as methanol, ethanol, propanol, or isopropanol, organic acids such as formic acid or acetic acid, aromatic hydrocarbons such as benzene, toluene or xylene, and ethers such as diethyl ether, tetrahydrofuran or dioxane can be cited. These can be used alone or two or more can be mixed. For reducing agent, sodium borohydride, sodium cyanoborohydride, pyridine-borane complexes and piperidine-borane complexes can be cited. About 0.9–2 molar equivalents, preferably 1–1.2 molar equivalents of General Formula (V) compound with respect to 1 mol of General Formula (VI) compound should be used. About 1–10 molar equivalents, preferably about 1–2 molar equivalents of reducing agent with respect to 1 mol of General Formula (VI) compound should be used. The reaction temperature is about 0–50°C. The reaction time is about 0.1–8 h, preferably about 0.5–2 h.

[0042]

(Process 6)

By reacting compounds represented by General Formula (III) above and compounds wherein R^2 in General Formula (V) is a lower alkyl group with condensing agent in appropriate solvent, compounds wherein R^2 in General Formula (I) is a lower alkyl group can be manufactured. There are no particular restrictions on solvents used here as long as they do not participate in the reaction. For example, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran or dioxane, halogenated hydrocarbons such as dichloromethane or chloroform, alkyl ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone, and aprotic polar solvents such as N,N-dimethylformaide,

N,N-dimethylacetamide, acetonitrile, and dimethyl sulfoxide can be cited. For condensing agents, triphenylphosphine – diethyl azodicarboxylate can be cited. About 0.9–2 molar equivalents, preferably about 1–1.2 molar equivalents of General Formula (V) compound with respect to 1 mol of General Formula (III) compound should be used. About 1–10 molar equivalents, preferably about 1–2 molar equivalents of condensing agent with respect to 1 mol of General Formula (III) should be used. The reaction temperature is about 0–50°C. The reaction time is about 1–48 h, preferably about 1–8 h.

[0043]

Moreover, compounds wherein R^2 in General Formula (I) is a hydrogen atom can be manufactured by alkaline hydrolysis in an appropriate solvent of compounds wherein R^2 in General Formula (I) is a lower alkyl group that are obtained by the above method. For solvent, water alone or water mixed with an organic solvent can be used. There are no particular restrictions on organic solvents as long as they do not participate in the reaction. For example, aromatic hydrocarbons such as benzene, toluene, or xylene, ethers such as diethyl ether, tetrahydrofuran or dioxane, halogenated hydrocarbons such as dichloromethane or chloroform, and aprotic polar solvents such as acetonitrile, dimethylformaide, dimethylacetamide and dimethyl sulfoxide can be cited. For alkaline compounds, for example, inorganic alkaline compounds like alkali metal carbonates such as sodium carbonate or potassium carbonate, alkali metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, and alkali methal hydroxides such as sodium hydroxide and potassium hydroxide can be cited. About 0.1–10 molar equivalents, preferably about 1–2 molar equivalents of alkaline compound with respect to 1 mol of compound where in R^2 in General Formula (I) is a lower alkyl group should be used. The reaction temperature is about 0°C – the boiling point of the solvent. The reaction time is about 0.5–48 h, preferably about 1–12 h.

[0044]

The phenylcarboxylic acid derivatives (I) of this invention obtained by the above methods can be isolated and purified by the conventional separating procedures, for example, column chromatography and recrystallization.

[0045]

The phenylcarboxylic acid derivatives (I) and their salts of this invention thus obtained act to inhibit fatty acid biosynthesis and cholesterol biosynthesis simultaneously and are useful as agents for treating hyperlipidemia, agents to prevent and treat atherosclerosis, an anti-obesity drugs, and medicines for reducing coronary artery disease.

[0046]

Application examples

This invention is explained in further detail giving reference examples, application examples and test examples below.

[0047]

(Reference Example 1)

Synthesis of 1-(4-chlorophenyl)-5-methyl-4-ethoxycarbonylpyrazole

N,N-dimethylformamide dimethylacetal (55.7 g, 0.46 mole) was added dropwise to ethyl acetoacetate (51.6 g, 0.39 mol). This was heated and stirred for 1 h at 100°C. After reaction, it was cooled and the residue obtained from concentrating under reduced pressure was distilled under reduced pressure. 63.7 g (87% yield; 156°C/0.2 torr) of N,N-dimethylaminomethylene ethyl acetoacetate ester were obtained. This compound (12.2 g, 66.3 mol) was added to a mixed solution of 4-chlorophenyl hydrazine hydrochloride (11.8 g, 66.3 mol), ethanol (100 mL) and acetic acid (1.9 g) and this was heated and stirred for 12 h at 60°C. After cooling, it was concentrated and extracted by adding ethyl acetate – water to the residue obtained. After the organic layer was rinsed with 1N hydrochloric acid, water, 1M aqueous solution of potassium carbonate, saline and water, it was dried with anhydrous magnesium sulfate. After filtering, it was concentrated under reduced pressure and n-hexane (500 mL) was added to the residue obtained. The deposited crystals were collected by filtration and 130 g (74% yield) of the target compound were obtained.

[0048]

(Reference Example 2)

Synthesis of 1-(4-chlorophenyl)-4-ethoxycarbonylpyrazole

To an ethanol (50 mL) solution of ethoxycarbonyl malonaldehyde (7.2 g, 50 mmol), a diethyl ether solution (200 mL) of 4-chlorophenyl hydrazine (8.5 g, 60 mmol) was added dropwise while cooling with ice. After stirring for 3 h at room temperature, the solvent was distilled off and the residue obtained was crystallized by adding ethanol. The deposited crystals were collected by filtration and 8.3 g (66% yield) of the target compound were obtained.

[0049]

(Reference Example 3)

Synthesis of 1-chlorophenyl-5-dimethylamino-4-ethoxycarbonylpyrazole

To an ethanol (50 mL) solution of ethoxymethylene ethyl cyanoacetate ester (1.69 g,

10 mmol), 4-chlorophenyl hydrazine (1.7 g, 12 mmol) was added and this was refluxed and stirred for 12 h. After the reaction, the solvent was distilled off and the residue obtained was crystallized by adding diethyl ether. Deposited crystals were collected by filtration and 2.2 g (82% yield) of 1-chlorophenyl-5-amino-4-ethoxycarbonylpyrazole were obtained. To a tetrahydrofuran solution (20 mL) of this compound (1.3 g, 5 mmol), 60% sodium hydride (0.44 g) was added while cooling with ice and this was stirred. After stirring for 30 min, methyl iodide (1.7 g, 12 mmol) was added and this was stirred for 12 h at room temperature. After reaction, it was extracted by adding an ethyl acetate – sodium bicarbonate aqueous solution. After the organic layer was rinsed with saline and water, it was dried with magnesium sulfate. After filtering, it was concentrated under reduced pressure and by recrystallizing the residue obtained using ether, and 1.4 g (95% yield) of the target compound were obtained.

[0050]

(Reference Example 4)

Synthesis of 1-chlorophenyl-3-dimethylamino-4-ethoxycarbonylpyrazole

To a xylene (80 mL) solution of phenyl hydrazine (10.8 g, 0.1 mol), benzaldehyde (10.6 g, 0.1 mol) was added and this was stirred at room temperature. After crystal deposition, ethoxymethylene ethyl cyanoacetate ester (20.3 g, 0.12 mol) was added and this was refluxed and stirred for 3 days. Crystals that deposited after they were first dissolved were collected by filtration and rinsed with diethyl ether to obtain white crystals (25 g). These crystals were added to a mixed solvent of concentrated hydrochloric acid (10 mL) and ethanol (60 mL) and this was refluxed and stirred for 15 min. After reaction, the solvent was distilled off. To the residue obtained, 10% aqueous potassium hydroxide solution (200 mL) was added while cooling with ice and this was extracted with chloroform. After rinsing the organic layer with saline and water, it was dried with magnesium sulfate. After filtration, it was concentrated under reduced pressure and by recrystallizing the residue obtained using ether, and 7.8 g (37% yield) of 1-chlorophenyl-3-amino-4-ethoxycarbonylpyrazole were obtained. To a tetrahydrofuran solution (50 mL) of this compound (6.2 g, 30 mmol), 60% sodium hydride (2..6 g) was added while cooling with ice and this was stirred. After stirring for 30 min, methyl iodide (10.2 g, 72 mmol) was added and this was stirred for 12 h at room temperature. After reaction, it was extracted by adding an ethyl acetate – sodium bicarbonate aqueous solution. After the organic layer was rinsed with saline and water, it was dried with magnesium sulfate. After filtration, 7.0 g (90% yield) of the target compound were obtained by concentrating under reduced pressure.

[0051]

(Reference Example 5)

Synthesis of 1-(4-chlorophenyl)-5-methyl-4-hydroxymethylpyrazole

To a tetrahydrofuran (50 mL) solution of aluminum lithium hydride (1 g, 26.4 mmol), a tetrahydrofuran (50 mL) solution of the 1-(4-chlorophenyl)-5-methyl-4-ethoxycarbonylpyrazole (10 g, 37.8 mmol) obtained in Reference Example 1 was added dropwise. After stirring for 30 min at room temperature, the reaction solution was added a little at a time to ice-cold dilute hydrochloric acid, after which the mixture was extracted by adding ethyl acetate. After the organic layer was rinsed with saline and water, it was dried with anhydrous magnesium sulfate. After filtration, 20 mL of diethyl ether were added to the residue obtained from concentrating under reduced pressure and the deposited crystals were collected by filtration to obtain 6.46 g (77% yield) of the target compound.

[0052]

(Reference Example 6)

Synthesis of 1-(4-chlorophenyl)-3-hydroxymethyl-5-methyl-1,2,4-triazole

To a tetrahydrofuran (15 mL) solution of aluminum lithium hydride (319 mg, 8.4 mmol), a tetrahydrofuran (15 mL) solution of 1-(4-chlorophenyl)-3-ethoxycarbonyl-5-methyl-1,2,4-triazole (3.19 g, 12 mmol) was added dropwise while cooling with ice. After this was stirred for 2 h, the reaction solution was added a little at a time to ice-cold 1N hydrochloric acid. Then, this was extracted by adding ethyl acetate. After rinsing the organic layer with saline and water, it was dried with anhydrous magnesium sulfate. After filtration, it was concentrated under reduced pressure and 20 mL of diethyl ether were added to the residue obtained. The deposited crystals were collected by filtration and 1.5 g (57% yield) of the target compound were obtained.

[0053]

(Application Example 1)

Synthesis of 1-(4-chlorophenyl)-5-methyl-4-(4'-methoxycarbonylphenoxy)methylpyrazole (Compound 1)

To a tetrahydrofuran (25 mL) solution of the 1-(4-chlorophenyl)-5-methyl-4-hydroxymethylpyrazole (6 g, 27 mmol) obtained in Reference Example 5, a tetrahydrofuran (5 mL) solution of thionyl chloride (3.2 g, 27 mmol) was added dropwise. After stirring for 30 min at room temperature, the reaction solution was added a little at a time to an ice-cold, saturated aqueous solution of sodium bicarbonate. Then, it was extracted by adding ethyl acetate. After the organic layer was rinsed with saline and water, it was dried

with anhydrous magnesium sulfate. After filtration, it was concentrated under reduced pressure and the 1-(4-chlorophenyl)-5-methyl-4-chloromethylpyrazole obtained was used for the next reaction without purification. A dimethylformamide solution (10 mL) of this crude product was added to a mixed dimethylformamide solution (70 mL) of p-hydroxybenzoic acid methyl ester (4.1 g, 27 mmol) and potassium carbonate (4.47 g, 32.3 mmol) and this was stirred for 24 h at 25°C. After reaction, ethyl acetate was added and insoluble matter was removed by filtration. The filtrate was concentrated under reduced pressure. To the residue obtained, water : methanol (40 mL, 1:1) was added and after heating and stirring, the mixture was cooled. The crystals obtained were collected by filtration and dried under reduced pressure to obtain 6.4 g (67% yield) of the target compound.

[0054]

① 元素分析（$C_{19}H_{17}N_2O_3Cl$として）

	C	H	N
② 計算値	63.96	4.80	7.85
③ 測定値	64.14	4.66	7.89

④ 融点：142－143℃

Key:
1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point:

(Application Example 2)

Synthesis of 1-(4-chlorophenyl)-5-methyl-4-(N-methyl-N-4'-ethoxycarbonylphenyl)aminomethylpyrazole (Compound 16)

To a chloroform (300 mL) solution of the 1-(4-chlorophenyl)-5-methyl-4-hydroxymethylpyrazole (10 g, 44.9 mmol) obtained in Reference Example 5, activated manganese dioxide (100 g, 1.15 mol) was added and this was stirred at room temperature. After reaction, insoluble matter was filtered with cerite. The 1-(4-chlorophenyl)-5-methyl-4-formylpyrazole obtained by concentrating the filtrate was used for the next reaction without purification. To an ethanol solution (30 mL) of this crude product, acetic acid (1 mL) and p-aminobenzoic acid ethyl ester (7.4 g, 44.9 mmol) were added. While cooling with ice, sodium cyanoborohydride (2.8 g, 44.9 mmol) was added a little at a time. After reaction, 97% formalin water (5 mL) was added, followed by adding a small amount of boron sodium cyanohydride (2.8 g, 44.9 mmol). After reaction, an ethyl acetate – sodium bicarbonate aqueous solution was added to the residue obtained from concentrating under reduced pressure and it was extracted. After the organic layer was rinsed with saline and water, it was dried with magnesium sulfate.

After filtration, the residue obtained from concentrating under reduced pressure was recrystallized using ethanol whereby 11.2 g (65% yield) of the target compound were obtained.

[0055]

① 元素分析（$C_{21}H_{22}N_3O_2Cl$として）

	C	H	N
② 計算値	65.71	5.78	10.95
③ 測定値	65.70	5.76	10.96

④ 融点：79－80℃

Key:
1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point:

(Application Example 3)

Synthesis of 1-(4-pyridyl)-5-methyl-4-(4'-methoxycarbonylphenoxy)methylpyrazole (Compound 7)

To a tetrahydrofuran solution (50 mL) of 1-(4-pyridyl)-5-methyl-4-hydroxymethylpyrazole (1.7 g, 8.99 mmol) obtained by the same method as Reference Example 5 and p-hydroxybenzoic acid methyl ester (1.67 g, 11 mmol), triphenylphosphine (2.35 g, 8.99 mmol) and diethylazodicarboxylic acid 3.9 mL, 40% toluene solution, 9 mmol) were added and this was stirred for 14 h at room temperature. After reaction, the residue obtained from concentrating under reduced pressure was purified by silica gel column chromatography (chloroform : methanol = 1 : 4). Residue obtained from concentrating the corresponding fractions was crystallized with diethyl ether and 1.2 g (41% yield) of the target compound were obtained.

[0056]

① 元素分析（$C_{18}H_{17}N_3O_3$として）

	C	H	N
② 計算値	66.86	5.30	13.00
③ 測定値	66.74	5.19	12.84

④ 融点：171－172℃

Key:
1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point

(Application Example 4)

Compounds 2 – 6, 8–15 and 17–19 shown in the table below were synthesized by the same method as for Application Examples 1–3.

[0057]

(Application Example 5)

Synthesis of 1-(4-chlorophenyl)-5-methyl-3-(4'-methoxycarbonylphenoxy)methyl-1,2,4-triazole (Compound 29)

To a tetrahydrofuran solution (30 mL) of the 1-(4-chlorophenyl)-3-hydroxymethyl-5-methyl-1,2,4-triazole (2.24 g, 10 mmol) obtained in Reference Example 6 and p-hydroxybenzoic acid methyl ester (1.52 g, 10 mmol), triphenylphosphine (3.15 g, 12 mmol) and diethylazodicarboxylic acid (5.22 g, 40% toluene solution, 12 mmol) were added and this was stirred for 14 h at room temperature. After reaction, the residue obtained from concentrating under reduced pressure was extracted by adding ethyl acetate. After the organic layer was rinsed with saline and water, it was dried with anhydrous magnesium sulfate. After filtration, the residue obtained from concentrating under reduced pressure was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1). By crystallizing the residue obtained from concentrating the corresponding fractions using diethyl ether, 2.6 g (74% yield) of the target compound were obtained.

[0058]

①元素分析（$C_{18}H_{16}N_3O_3Cl$として）

	C	H	N
②計算値	60.42	4.51	11.74
③測定値	60.35	4.50	11.76

④ 融点：139－140℃

Key:
1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point:

(Application Example 6)

Synthesis of 2-(4-chlorophenyl)-4-(2-(4'-methoxycarbonylphenoxy)ethyl)thiazole (Compound 32)

To a tetrahydrofuran solution (50 mL) of 2-(4-chlorophenyl)-4-(2-hydroxyethyl)thiazole (1 g, 4.18 mmol) and p-hydroxybenzoic acid methyl ester (699 mg, 4.59 mmol), triphenylphosphine (1 g, 5.02 mmol) and diethylazodicarboxylic acid (2.2 mL, 40% toluene

solution, 5.02 mmol) were added and this was stirred for 14 h at room temperature. After reaction, the residue obtained from concentrating under reduced pressure was extracted by adding ethyl acetate and water. After rinsing the organic layer with a 1N NaOH aqueous solution and saturated saline, it was dried with magnesium sulfate. After filtration, the residue obtained from concentrating under reduced pressure was crystallized using methanol whereby 1.1 g (70% yield) of the target compound were obtained.

[0059]

①元素分析（$C_{19}H_{16}NO_3SCl$として）

	C	H	N
②計算値	61.04	4.31	3.75
③測定値	60.87	4.28	3.74

④融点：155－156℃

Key: 1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point

(Application Example 7)

Synthesis of 2-(4-chlorophenyl)-4-(4'-methoxycarbonylphenoxy)methylthiazole (Compound 31)

An acetone (50 mL) solution of p-chlorothiobenzamide (5 g, 29.1 mmol) and α, α'-dichloroacetone (3.7 g, 29.1 mmol) was stirred for 3 h at room temperature. The deposited crystals were collected by filtration. Crude product rinsed with acetone was refluxed and stirred in methanol (50 mL) for 1 h. The crude product 2-(4-chlorophenyl)-4-chloromethylthiazole obtained by concentrating the reaction mixture under reduced pressure was used for the next reaction without purification. A dimethylformamide solution (10 mL) of this crude product was added to a mixed dimethylformamide solution (70 mL) of p-hydroxybenzoic acid methyl ester (3.8 g, 25 mmol) and potassium carbonate (5.2 g, 37.7 mmol) and this was stirred for 24 h at room temperature. After reaction, the residue obtained from concentrating under reduced pressure was extracted by adding ethyl acetate and water. After rinsing the organic layer with a 1N NaOH aqueous solution, water and saline, it was dried with magnesium sulfate. After filtration, the residue obtained from concentrating under reduced pressure was crystallized using methanol whereby 6.2 g (61% yield) of the target compound were obtained.

[0060]

①元素分析（$C_{18}H_{14}NO_{3}SCl$として）

	C	H	N
②計算値	60.08	3.92	3.89
③測定値	60.09	3.74	3.88

④融点：118－120℃

Key: 1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point

(Application Example 8)

Compound 33 shown in the table below was synthesized by the same method as in Application Examples 6–7.

[0061]

(Application Example 9)

Synthesis of 1-(4-chlorophenyl)-5-methyl-4-(4'-carboxyphenoxy)methylpyrazole (Compound 20)

To a methanol : dioxane (200 mL, 1 : 1) solution of the compound of Application Example 1 (5.1 g, 14.9 mmol), a 0.2N NaOH aqueous solution (100 mL) was added and this was heated and stirred for 5 h at 70°C. After reaction, the solvent was distilled off. Cold dilute hydrochloric acid was added and this was extracted using ethyl acetate. After the organic layer was rinsed with saline and water, it was dried with anhydrous magnesium sulfate. After filtration, 20 mL of diethyl ether were added to the residue obtained from concentrating under reduced pressure. The deposited crystals were collected by filtration and dried to obtain 4.99 g (97.3% yield) of the target compound.

[0062]

①元素分析（$C_{18}H_{15}N_{2}O_{3}Cl$として）

	C	H	N
②計算値	63.07	4.41	8.17
③測定値	63.07	4.39	8.10

④融点：201－202℃

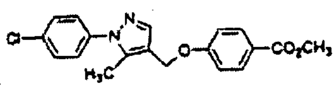
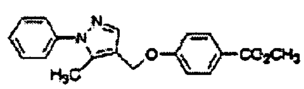
Key: 1 Elemental analysis
2 Calculated values
3 Measured values
4 Melting point:

(Application Example 10)

Compounds 21–28, 30, 34 and 35 shown in the table below were synthesized by the same method as in Application Example 9.

[0063]

[Table 1]

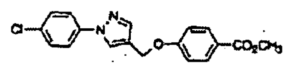
①	化合物 1 				^{1}H NMR ($CDCl_3$) : δ 2.36(3H,s), 3.89(3H,s), 5.00(2H,s), 7.01(2H,d,J=9.0Hz,), 7.40(2H,d,J=8.8Hz,), 7.46(2H,d,J=8.8Hz,), 7.71(1H,s,), 8.02(2H,d,J=8.8Hz,)
②	融点 142 - 143 °C				
③	元素分析 $C_{19}H_{17}ClN_2O_3$				
		C	H	N	
④	計算値	63.96	4.80	7.85	
⑤	測定値	64.14	4.66	7.89	
①	化合物 2 				^{1}H NMR (DMSO-d_6) : δ 2.34 (3H, s,), 3.82 (3H, s), 5.09 (2H, s), 7.15 (2H, d, J = 9Hz), 7.4-7.6 (5H, m), 7.76 (1H, s), 7.93 (2H, d, J = 9Hz)
②	融点 124 - 125 °C				
③	元素分析 $C_{19}H_{18}N_2O_3$				
		C	H	N	
④	計算値	70.79	5.63	8.69	
⑤	測定値	70.99	5.51	8.75	

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0064]

[Table 2]

① 化合物 3



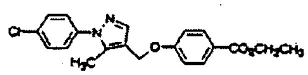
② 融点 152 - 153 °C

③ 元素分析 $C_{18}H_{15}ClN_2O_3$

	C	H	N
④ 計算値	63.07	4.41	8.17
⑤ 測定値	63.14	4.20	8.15

^{1}H NMR (DMSO-d_6) : δ
3.82 (3H, s)
5.15 (2H, s)
7.15 (2H, d, J = 9Hz)
7.57 (2H, d, J = 9Hz)
7.87 (2H, d, J = 9Hz)
7.89 (1H, s)
7.93 (2H, d, J = 9Hz)
8.67 (1H, s)

① 化合物 4



② 融点 122 - 124 °C

③ 元素分析 $C_{20}H_{19}ClN_2O_3$

	C	H	N
④ 計算値	64.78	5.16	7.55
⑤ 測定値	65.09	5.11	7.66

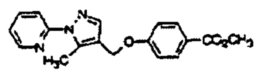
^{1}H NMR ($CDCl_3$) : δ
1.39(3H,t,J=7.3Hz),
2.36(3H,s),
4.35(2H,q,J=7.3Hz),
5.00(2H,s),
7.00(2H,d,J=8.9Hz,),
7.40(2H,d,J=8.9Hz,),
7.45(2H,d,J=8.9Hz,),
7.45(1H,s,),
8.02(2H,d,J=9.2Hz,)

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0065]

[Table 3]

① 化合物 5



② 融点 125 - 126 °C

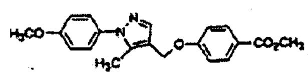
③ 元素分析 $C_{18}H_{17}N_3O_3$

	C	H	N
④ 計算値	66.86	5.30	13.00
⑤ 測定値	67.05	5.17	13.05

^{1}H NMR ($CDCl_3$) : δ

2.70(3H,s),
3.89(3H,s),
5.02(2H,s),
7.02(2H,d,J=8.9Hz,),
7.23(1H,m),
7.72(1H,s),
7.80~7.90(2H,m),
8.01(2H,d,J=9.2Hz),
8.46(1H,m)

① 化合物 6



② 融点 129 - 130 °C

③ 元素分析 $C_{20}H_{20}N_2O_4$

	C	H	N
④ 計算値	68.17	5.72	7.95
⑤ 測定値	68.07	5.70	7.93

^{1}H NMR (DMSO-d_6) : δ

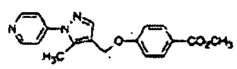
2.2(3H, S) ,
3.8(3H, S,),
5.0(2H, S),
7.0(2H, d, J = 8.0Hz)
7.1(2H, d, J = 8.0Hz)
7.4(2H, d, J = 8.0Hz)
7.7(1H, S)
7.9(2H, d, J = 8.0Hz)

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0066]

[Table 4]

① 化合物 7



② 融点 171 - 172℃

③ 元素分析 $C_{18}H_{17}N_3O_3$

	C	H	N
④ 計算値	66.86	5.30	13.00
⑤ 測定値	66.74	5.19	12.84

^{1}H NMR ($CDCl_3$) : δ

2.5(3H, S) ·

3.9(3H, S.),

5.0(2H, S),

7.0(2H, d, J = 8.0Hz) ,

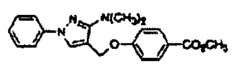
7.5(2H, d, J = 6.3Hz) ,

7.7(1H, S) ,

8.0(2H, d, J = 8.0Hz) ,

8.7(2H, d, J = 6.1Hz)

① 化合物 8



② 融点 159 - 161 ℃

③ 元素分析 $C_{20}H_{21}N_3O_3$

	C	H	N
④ 計算値	68.36	6.02	11.96
⑤ 測定値	68.42	6.02	12.08

^{1}H NMR (DMSO-d_6) : δ

2.88 (6H, s), 3.82 (3H, s),

5.08 (2H, s)

7.16 (2H, d, J = 9Hz)

7.19 (1H, d, J = 7.5Hz)

7.44 (2H, dd, J = 8Hz,7.5Hz)

7.70 (2H, d, J = 8Hz)

7.93 (2H, d, J = 9Hz)

Key:

1 Compound ___

2 Melting point

3 Elemental analysis

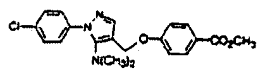
4 Calculated values

5 Measured values

[0067]

[Table 5]

① 化合物 9



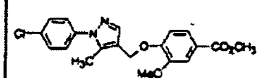
^1H NMR (DMSO-d_6) : δ 2.66 (6H, s), 3.82 (3H, s), 5.11 (2H, s), 7.15 (2H, d, J = 9Hz), 7.55 (2H, d, J = 9Hz), 7.68 (1H, s), 7.70 (2H, d, J = 9Hz), 7.93 (2H, d, J = 9Hz)

② 融点 150 - 151 °C

③ 元素分析 $C_{20}H_{20}ClN_3O_3$

	C	H	N
④ 計算値	62.26	5.22	10.89
⑤ 測定値	62.22	5.23	10.91

① 化合物 1 0



^1H NMR ($CDCl_3$) : δ 2.36(3H,s), 3.90(3H,s), 3.91(3H,s), 5.06(2H,s), 7.03(1H,d,J=8.6Hz), 7.39(2H,d,J=8.9Hz), 7.45(2H,d,J=8.6Hz), 7.57(1H,d, J=2.0Hz), 7.68(1H,dd,J=2.0,8.6Hz), 7.71(1H,s)

② 融点 179 - 180°C

③ 元素分析 $C_{20}H_{19}ClN_2O_4$ 1/5 H_2O

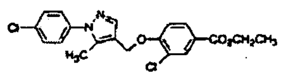
	C	H	N
④ 計算値	66.86	5.30	13.00
⑤ 測定値	66.74	5.19	12.84

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0068]

[Table 6]

①化合物１１



^{1}H NMR ($CDCl_3$) : δ

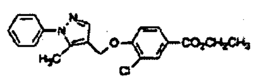
1.39(3H,t,J=7.3Hz),
2.39(3H,s),
4.37(2H,q,J=7.3Hz),
5.10(2H,s),
7.09(1H,d,J=8.6Hz),
7.41(2H,d,J=8.6Hz),
7.46(2H,d,J=8.9Hz),
7.71(1H,s)
7.96(1H,dd,J=2.3,8.6Hz)
8.07(1H,d, J=2.0Hz)

②融点 171 - 172 °C

③元素分析 $C_{20}H_{18}Cl_2N_2O_3$

	C	H	N
④計算値	59.27	4.48	6.91
⑤測定値	59.20	4.46	6.91

①化合物１２



^{1}H NMR ($CDCl_3$) : δ

1.39(3H, t),
2.39(3H, S)
4.36(2H, q, J = 7.3Hz),
5.12(2H, S),
7.1(2H, d, J = 8.0Hz) ,
7.37-7.52(2H, m) ,
7.71(1H, S)
7.96(1H, dd, J = 2.3, 8.6 Hz) ,
8.07(1H, d, J = 2.0Hz)

②融点 144 - 145 °C

③元素分析 $C_{20}H_{19}ClN_2O_3$

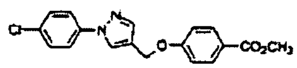
	C	H	N
④計算値	64.78	5.16	7.55
⑤測定値	64.76	5.14	7.57

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0069]

[Table 7]

① 化合物 1 3



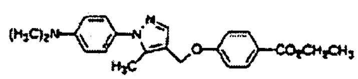
^{1}H NMR (DMSO-d_6) : δ
3.48 (1H; br.s), 5.06 (2H, s)
6.95 (2H, d, J = 9Hz)
7.56 (2H, d, J = 8.5Hz)
7.83 (2H, d, J = 8.5Hz)
7.87 (1H, s)
7.87 (2H, d, J = 9Hz)
8.67 (1H, s)

② 融点 243 - 244°C

③ 元素分析 $C_{17}H_{13}ClN_2O_3$

		C	H	N
④	計算値	62.11	3.99	8.52
⑤	測定値	61.98	3.93	8.42

① 化合物 1 4



^{1}H NMR ($CDCl_3$) : δ
1.38(3H, t, J = 7.0Hz),
2.3(3H, S,) ,
3.0(6H, S),
4.3(2H, q, J = 7.0Hz),
4.99(2H, S),
6.7(2H, d, J = 9.0Hz),
7.0(2H, d, J = 8.7Hz)
7.2(2H, d, J = 9.0Hz),
7.6(1H, S) ,
8.0(2H, d, J = 8.2Hz)

② 融点 151 - 152 °C

③ 元素分析 $C_{18}H_{17}N_3O_3$ 1/4 H_2O

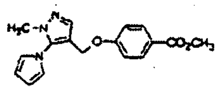
		C	H	N
④	計算値	69.64	6.64	11.07
⑤	測定値	69.42	6.61	11.01

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0070]

[Table 8]

① 化合物１５



② 融点	136 - 137°C			^1H NMR (DMSO-d_6) : δ
③ 元素分析	$C_{17}H_{17}N_3O_3$			3.64 (3H, s)
	C	H	N	3.80 (3H, s)
④ 計算値	65.58	5.50	13.50	4.86 (2H, s)
⑤ 測定値	65.46	5.56	13.39	6.32-6.34 (1H, m)
				7.00 (2H, d, J = 9Hz)
				7.03-7.06 (1H, m)
				7.71 (1H, s)
				7.87 (2H, d, J = 9Hz)

① 化合物１６

② 融点	79 - 80 °C			^1H NMR ($CDCl_3$) : δ
③ 元素分析	$C_{21}H_{22}ClN_3O_2$			1.37(3H,t,J=7.3Hz),
	C	H	N	2.27(3H,s),
④ 計算値	65.51	5.78	10.95	3.04(3H,s),
⑤ 測定値	65.70	5.76	10.96	4.33(2H,q,J=7.3Hz),
				4.45(2H,s),
				6.77(2H,d,J=9.2Hz),
				7.34(2H,d,J=9.2Hz),
				7.44(2H,d,J=9.2Hz),
				7.45(1H,s),
				7.93(2H,d,J=9.2Hz)

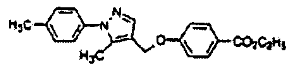
Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0071]

[Table 9]

①

化合物１７



②

融点　１１５－１１７℃

③

元素分析　$C_{21}H_{22}N_2O_3 \cdot 1/5H_2O$

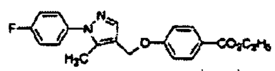
	C	H	N
④ 計算値	71.25	6.38	7.91
⑤ 測定値	71.28	6.33	7.73

^{1}H NMR ($CDCl_3$) : δ

1.39 (3H,t,J=7.3Hz)
2.34 (3H,s)
2.42 (3H,s)
4.35 (2H,q,J=7.3Hz)
5.01 (2H,s)
7.02 (2H,d,J=8.9Hz)
7.27 (2H,d,J=8.6Hz)
7.31 (2H,d,J=8.6Hz)
7.68 (1H,s)
8.01 (2H,d,J=8.9Hz)

①

化合物１８



②

融点　１２０－１２２℃

③

元素分析　$C_{20}H_{19}FN_2O_3$

	C	H	N
④ 計算値	67.79	5.40	7.90
⑤ 測定値	67.89	5.44	7.82

^{1}H NMR ($CDCl_3$) : δ

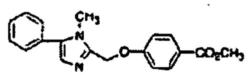
1.39 (3H,t,J=7.3Hz)
2.34 (3H,s)
4.36 (2H,q,J=7.3Hz)
5.00 (2H,s)
7.02 (2H,d,J=8.9Hz)
7.18 (2H,dd,J=8.2,8.9Hz)
7.41 (2H,dd,J=4.6,8.9Hz)
7.70 (1H,s)
8.02 (2H,d,J=8.9Hz)

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0072]

[Table 10]

①化合物１９



^1H NMR ($CDCl_3$) : δ

3.7(3H, S), 3.88(3H, S), 5.2(2H, S), 7.1(2H, d, J = 8.8Hz), 7.2(1H, S), 7.3(5H, m), 8.0(2H, d, J = 8.8Hz)

② 融点 139 - 140°C

③ 元素分析 $C_{19}H_{18}N_2O_3$

	C	H	N
④ 計算値	70.79	5.63	8.69
⑤ 測定値	70.79	5.56	8.65

①化合物２０

^1H NMR (DMSO-d_6) : δ

2.2(3H, S), 5.0(2H, S), 7.1(2H, d, J = 8.0Hz), 7.5(4H, S), 7.7(1H, S), 7.9(2H, d, J = 8.0Hz), 12.6(1H, b)

② 融点 201 - 202°C

③ 元素分析 $C_{18}H_{15}ClN_2O_3$

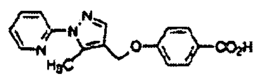
	C	H	N
④ 計算値	63.07	4.41	8.17
⑤ 測定値	63.07	4.39	8.10

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0073]

[Table 11]

① 化合物２１



^{1}H NMR (DMSO-d_6) : δ

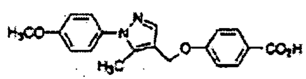
2.71(3H,s),
5.04(2H,s),
7.05(2H,d,J=8.9Hz),
7.24(1H,m),
7.74(1H,s),
7.80~7.90(2H,m),
8.08(2H,d,J=9.2Hz),
8.45(1H,m)

② 融点　182 - 184℃

③ 元素分析　$C_{17}H_{15}N_3O_3$

	C	H	N
④ 計算値	66.01	4.89	13.58
⑤ 測定値	66.33	4.74	13.66

① 化合物２２



^{1}H NMR (DMSO-d_6) : δ

2.2(3H, S),
3.8(3H, S),
5.0(2H, S),
7.0(2H, d, J = 8.0Hz),
7.1(2H, d, J = 8.0Hz),
7.4(2H, d, J = 8.0Hz),
7.7(1H, S),
7.9(2H, d, J = 8.0Hz),
12.5(1H, b)

② 融点　187 - 188°C

③ 元素分析　$C_{19}H_{18}N_2O_4$

	C	H	N
④ 計算値	67.45	5.36	8.28
⑤ 測定値	67.46	5.28	8.26

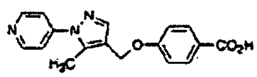
~~【表12】~~

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0074]

[Table 12]

① 化合物２３



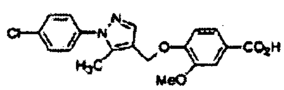
② 融点 243 - 245℃

③ 元素分析 $C_{17}H_{15}N_3O_3$

	C	H	N
④ 計算値	66.01	4.89	13.58
⑤ 測定値	66.28	4.61	13.39

^{1}H NMR (DMSO-d_6) : δ
2.6(3H, S),
5.1(2H, S),
7.1(2H, d, J = 8.2Hz),
7.9(2H, d, J = 8.2Hz),
8.0(1H, S),
8.0(2H, d, J = 5.8Hz),
8.8(2H, d, J = 5.8Hz)

① 化合物２４



② 融点 237 - 238°C

③ 元素分析 $C_{19}H_{17}ClN_2O_4$

	C	H	N
④ 計算値	61.21	4.60	7.51
⑤ 測定値	61.48	4.61	7.49

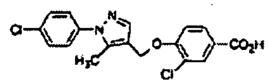
^{1}H NMR (DMSO-d_6) : δ
2.35(3H,s),
3.79(3H,s),
5.05(2H,s),
7.25(1H,d,J=8.2Hz),
7.46(1H,d, J=2.0Hz),
7.60(5H,m),
7.77(1H,s),
12.69(1H,brs)

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0075]

[Table 13]

①化合物２５



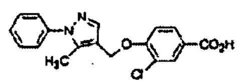
②融点　210 - 211℃

③元素分析　$C_{18}H_{14}Cl_2N_2O_3$

	C	H	N
④計算値	57.31	3.74	7.43
⑤測定値	57.20	3.71	7.33

^{1}H NMR (DMSO-d_6) : δ
2.38(3H,s),
4.50(2H,s),
7.00(2H,d,J=9.2Hz),
7.60(4H,m),
7.80(1H,s),
7.91～7.93(2H,m,J=9.2Hz)

①化合物２６



②融点　189 - 191°C

③元素分析　$C_{18}H_{15}ClN_2O_3$　1/4 H_2O

	C	H	N
④計算値	62.25	4.50	8.07
⑤測定値	62.47	4.38	7.98

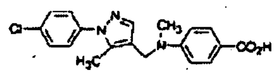
^{1}H NMR (DMSO-d_6) : δ
2.37(3H, S),
5.21(2H, S),
7.46(2H, m),
7.54(4H, m),
7.78(1H, S),
7.92(2H, m)

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0076]

[Table 14]

① 化合物２７



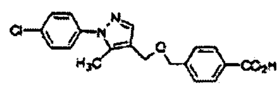
^{1}H NMR (DMSO-d_6) : δ 2.33(3H,s), 3.02(3H,s), 4.50(2H,s), 7.00(2H,d,J=8.9Hz), 7.47(1H,s), 7.54(2H,d,J=8.9Hz), 7.57(2H,d,J=8.9Hz), 7.76(2H,d,J=9.2Hz)

② 融点 213 - 215°C

③ 元素分析 $C_{19}H_{18}ClN_3O_2$

	C	H	N
④ 計算値	64.14	5.10	11.81
⑤ 測定値	64.06	5.15	11.76

① 化合物２８



^{1}H NMR (DMSO-d_6) : δ 2.30(3H,s), 4.46(2H,s), 4.59(2H,s), 7.46(2H,d,J=7.9Hz), 7.58(4H,m), 7.67(1H,s), 7.92(2H,d, J=8.2Hz)

② 融点 162 - 163°C

③ 元素分析 $C_{19}H_{17}ClN_2O_3$

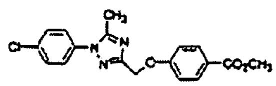
	C	H	N
④ 計算値	63.96	4.80	7.85
⑤ 測定値	64.08	4.78	7.65

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0077]

[Table 15]

① 化合物 2 9



^1H NMR (DMSO-d_6) : δ

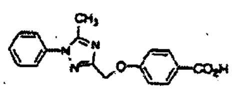
2.51 (3H, s)
3.82 (3H, s)
5.21 (2H, s)
7.18 (2H, d, J = 9Hz)
7.65 (4H, s)
7.93 (2H, d, J = 9Hz)

② 融点 139 - 140℃

③ 元素分析 $C_{18}H_{16}ClN_3O_3$

	C	H	N
④ 計算値	60.42	4.51	11.74
⑤ 測定値	60.35	4.50	11.76

① 化合物 3 0



^1H NMR (DMSO-d_6) : δ

2.49 (3H, s)
5.19 (2H, s)
7.15 (2H, d, J = 9Hz)
7.65 (4H, s)
7.90 (2H, d, J = 9Hz)
12.65 (1H, s)

② 融点 212 - 214℃

③ 元素分析 $C_{17}H_{14}ClN_3O_3$

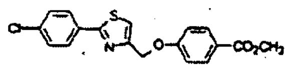
	C	H	N
④ 計算値	59.40	4.10	12.22
⑤ 測定値	59.69	4.14	12.09

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0078]

[Table 16]

① 化合物31



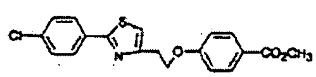
^1H NMR ($CDCl_3$): δ 3.89(3H,s), 5.30(2H,s), 7.04(2H,d,J=8.9Hz), 7.33(1H,s), 7.43(2H,d,J=8.9Hz), 7.89(2H,d,J=8.9Hz), 8.01(2H,d,J=8.9Hz)

② 融点 118 - 120°C

③ 元素分析 $C_{18}H_{14}ClNO_3S$

	C	H	N
④ 計算値	60.08	3.92	3.89
⑤ 測定値	60.09	3.74	3.88

① 化合物32



^1H NMR ($CDCl_3$): δ 3.32(2H,m), 3.88(3H,s), 4.41(2H,m), 6.94(2H,d,J=8.9Hz), 7.07(1H,s), 7.41(2H,d,J=8.6Hz), 7.86(2H,d,J=8.6Hz), 7.97(2H,d,J=8.6Hz)

② 融点 155 - 156°C

③ 元素分析 $C_{19}H_{16}ClNO_3S$

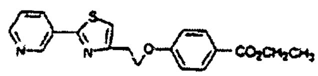
	C	H	N
④ 計算値	61.04	4.31	3.75
⑤ 測定値	60.87	4.28	3.74

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0079]

[Table 17]

① 化合物 3 3



^{1}H-NMR(CDCl$_3$): δ

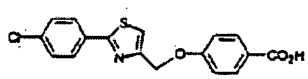
② 融点 100 - 101°C

③ 元素分析 $C_{19}H_{18}N_2O_3S$

	C	H	N
④ 計算値	64.39	5.12	7.90
⑤ 測定値	64.48	5.09	7.90

1.38(3H,t,J=7.3Hz), 3.34(2H,m), 4.35(2H,q,J=7.3Hz), 4.43(2H,m,), 6.94(2H,d,J=8.9Hz), 7.14(1H,s), 7.38(1H,dd,J=4.9,7.9Hz), 7.99(2H,d,J=8.9Hz), 8.22(1H,dt,J=2.0,7.9Hz), 8.65(1H,dd,J=2.0,7.9Hz), 9.15(1H,d,J=1.7Hz)

① 化合物 3 4



^{1}H NMR (DMSO-d$_6$) : δ

② 融点 237 - 238°C

③ 元素分析 $C_{17}H_{12}ClNO_3S$

	C	H	N
④ 計算値	59.05	3.50	4.05
⑤ 測定値	58.92	3.26	4.05

5.31(2H,s), 7.17(2H,d,J=8.9Hz), 7.58(2H,d,J=8.6Hz), 7.88(2H,d,J=8.9Hz), 7.93(1H,s), 7.97(2H,d,J=8.6Hz)

Key:
1 Compound ___
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0080]

[Table 18]

① 化合物35

②	融点	234.5 - 235.5°C			^1H NMR (DMSO-d_6) : δ
③	元素分析	$C_{18}H_{14}ClNO_3S$			3.25(2H,m), 4.43(2H,m), 7.05(2H,d,J=8.9Hz), 7.55(1H,s), 7.57(2H,d,J=8.2Hz), 7.87(2H,d,J=8.6Hz), 7.94(2H,d,J=8.2Hz), 12.6(1H,brs)
		C	H	N	
④	計算値	60.08	3.92	3.89	
⑤	測定値	59.75	3.88	3.84	

Key: 1 Compound 35
2 Melting point
3 Elemental analysis
4 Calculated values
5 Measured values

[0081]

Test examples

Effects on sterol and fatty acid biosynthetic systems using rat liver slices and triglyceride- and cholesterol-reducing effects using rats were studied by the methods given below.

[0082]

Test Example 1

Effects on sterol and fatty acid biosynthetic systems using rat liver fragments (in vitro test)

Tests were conducted according to the following procedures consulting the following reference.

[0083]

Endo, A., Tsujita, Y., Kuroda, M. and Tanzawa, K., Eur. J. Biochem., 77, 31–36 (1977).

[0084]

That is, after sacrificing male S.D. rats (body weight approximately 200 g) by decapitation, livers were quickly excised and thoroughly perfused with ice-cold Krebs-Ringer bicarbonate buffer. In 1 mL of Krebs-Ringer bicarbonate buffer containing [1-^{14}C]acetic acid (74 kBq/2 μmol) and test compound prepared in various concentrations, 100 mg of liver slices were added. In a mixed gas of 95% O_2 – 5% CO_2, the reaction was conducted for 2 h at 37°C. After cooling, 2 mL of petroleum ether were added and the sterol fraction was shaken and extracted. After concentrating, 1 mL of a 1% digitonin solution was added. After allowing to stand, the sterol fraction obtained as precipitate by centrifugation procedures was rinsed several times with organic solvent. After solubilizing in 1 mL of acetic acid, the radioactivity was determined. The test compound concentration (IC_{50}) that inhibited up to 50% of the radioactivity of the control group from which test compound was excluded was determined.

[0085]

By the same method, the radioactivity of the fatty acid fraction obtained by hydrochloric acid treatment from the lower petroleum ether layer of the above procedure was determined.

[0086]

The results obtained are shown in the following table.

[0087]

[Table 19]

①

脂肪酸、ステロール阻害活性（ラット肝スライス）		
② 化合物番号	In vitro（IC₅₀ μm）	
	ステロール ③	脂肪酸 ④
2	14.44	5.34
4	8.36	7.49
20	17.2	7.13
29	25.84	11.71

Key: 1 Fatty acid, sterol-inhibiting activity (rat liver slice)
2 Compound No.
3 Sterol
4 Fatty acid

[0088]

Test Example 2

Triglyceride- and cholesterol-reducing action using rats (in vivo test)

To male S.D. rats (5 week old, 8 animals) being fed a normal diet, a medicating solution of 30 mg/5 mL drug in a 0.5% hydroxypropylmethylcellulose aqueous solution/kg was forcibly given orally into the stomach for 7 consecutive days. Meanwhile, to the control group (male S.D. rats, 5 week old, 8 animals), a hydroxypropylmethylcellulose aqueous solution alone was similarly given. 16 h after the final dose, blood was collected from the abdominal vena cava under ether anesthesia and serum lipid categories (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), phospholipids (PL), triglycerides (TG)) were measured.

[0089]

Very low density lipoprotein cholesterol ((V)LDL-C), atherosclerosis index (AI) and rate of change were calculated by the following equations.

[0090]

(V) LDL・C＝TC－HDL・C　AI＝ (V) LDL・C／HDL・C

Rate of change (%) = {(measured value for medicated group/measured value for control group)-1}x100

Results obtained are given in the following table.

[0091]

[Table 20]

① 化合物番号		TC	(V)LDL-C	HDL-C	AI	TG	PL
② 2	実測値(mg/dl)	69.0	19.7	49.3	0.4	78.6	121.4
	変化率 (%)③	-7.0	**-32.3	9.3	**-38.6	**-43.5	**-14.7
④ 4	実測値(mg/dl)	69.4	22.6	46.8	0.49	70.6	119.8
	変化率 (%)⑤	-6.5	**-22.3	3.8	*-24.6	**-49.3	**-15.9
⑥ 20	実測値(mg/dl)	58.9	17.9	41	0.45	61.4	105.3
	変化率 (%)⑦	**-20.6	**-38.5	-9.1	**-30.8	**-55.9	**-26.1
Control	実測値(mg/dl ⑧	74.2	29.1	45.1	0.65	139.2	142.4

*: p<0.05 **: p<0.01 (Dunnet's test)

Key:
1 Compound No.
2 Measured value (mg/dL)
3 Rate of change (%)
4 Measured value (mg/dL)

5 Rate of change (%)
6 Measured value (mg/dL)
7 Rate of change (%)
8 Measured value (mg/dL)

[0092]

Effects of the invention

As shown in the in vitro test results above, the phenylcarboxylic acid derivatives (I) and their salts of this invention act to inhibit fatty acid biosynthesis and cholesterol biosynthesis. And as shown in the in vivo test results above, they simultaneously reduce triglycerides (TG) and very low density lipoprotein cholesterol ((V)LDL-C, bad cholesterol) in the blood. Meanwhile, they can reduce the atheroscloerosis index without reducing high density lipoprotein cholesterol (HDL-C, good cholesterol). For this reason, the phenylcarboxylic acid derivatives (I) and their salts of this invention are useful as agents for treating hyperlipidemia, agents for preventing and treating atherosclerosis, anti-obesity drugs and medicines for reducing coronary artery disease.